A version of these claims showing the specific amendments made herein is attached.

REMARKS

Claims 1-14, 17, 19-24, 26, 27, 29 and 31 are pending in the present application. Claims 1-13, 21 and 22 have been withdrawn from consideration based on a restriction requirement.

Claims 14, 17, 19, 20, 23, 24, 26, 27, 29 and 31 remain under active consideration. Based on the comments made by the Examiner in the January 2, 2002 Office Action, it is respectfully submitted that the amendments made herein place this application in form for allowance.

By way of review, the present invention provides a quick and effective method for assessing in a patient whether there has been axonal damage resulting from a traumatic head injury, and the extent of that damage. Until now, there has been no effective, minimally invasive procedure for quickly determining that information which, of course, can be critical in an emergency room setting. In this method, a patient suspected of having such traumatic head injury, such as a blow to the head sustained in a car accident, provides a sample of cerebrospinal fluid. The presence in that fluid of specific tau proteins are then determined using a monoclonal antibody raised against those proteins, and the levels of those proteins in the fluid are compared to control samples representing both damaged and undamaged states. This comparison yields information regarding whether there has been a traumatic head injury and the extent of that injury in the patient.

The objections raised by the Examiner in the Office Action will now be considered sequentially, referring to the paragraph numbers used by the Examiner.

Paragraph 8. The Examiner has rejected the claims, under the first paragraph of 35 U.S.C. § 112, contending that the terms "traumatic central nervous system injury" and "in the range of from about 30 to about 50 kDa" are not supported by the disclosure.

Claims 14 and 31 have been amended to utilize the phrase "traumatic head injury" in place of "traumatic central nervous system injury." Antecedent basis for this amendment is found page 2 of the present application where it refers to "head injury" (see lines 6 and 9), "head trauma" (see lines 12 and 14), and combines a discussion of head trauma and CNS injury (see line 18). The term "traumatic head injury" is a term well-known and well-

accepted in the art – see the attached materials from the U.S. Center for Disease Control and the Missouri Head Injury Advisory Council which utilize and define the term.

Further, claims 17 and 24 have been amended to delete the word "about" from the definition of the molecular weight of the tau protein fragments.

In light of these amendments, it is submitted that the currently pending claims are fully supported by the specification and it is respectfully requested that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Paragraph 9. The Examiner has rejected the claims of the present application, under the second paragraph of 35 U.S.C. § 112, contending that the use of the phrase "in the form of an isoform of tau protein of SEQ ID NO:1" renders the claims ambiguous. Applicants have amended claims 14 and 31 in the manner suggested by the Examiner. In light of that amendment, it is requested that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Paragraph 10. Finally, the Examiner has rejected the claims, under 35 U.S.C. § 102(b), contending that they are anticipated by the disclosure of Vandermeeren et al. (WO 94/13795) which deals with the detection of Alzheimer's Disease. This rejection is respectfully traversed in view of the amendments to claims 14 and 31.

The claims in the present application relate to an assay to detect the presence and extent of "traumatic head injury." "Traumatic head injury" is an art-recognized term which is defined as an injury caused by a sudden insult to the brain or head (see the attached excerpt from the Missouri Head Injury Advisory Council). Such injuries would include, for example, a head hitting the steering wheel of a car in a car accident, a head being hit by a baseball bat, or a bullet wound to the head. It very clearly would not include Alzheimer's Disease which is not caused by a sudden insult to the head and therefore would not be considered a "traumatic head injury." If there is any doubt as to the correctness of that conclusion, the Examiner's attention is directed to the attached Missouri excerpt which states that a "traumatic head injury" is "not of a degenerative nature." Since Alzheimer's Disease is degenerative in nature (see page 2, line 21 of the present application: "Alzheimer's Disease is a progressive degenerative disease . . ."), it clearly is not a "traumatic head injury." While Applicants are sure that when a patient gets Alzheimer's Disease it is emotionally traumatic for the patient's family, as the Examiner has pointed out, that does not make Alzheimer's Disease a "traumatic head injury" as that term is understood in the art. Since Vandermeeren et al. does

not disclose or suggest any assays for traumatic head injuries, the present invention, as defined by the claims herein, is patentable over it. Accordingly, it is respectfully requested that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Reconsideration and allowance of the present application is requested in view of the amendments and remarks made herein. Applicants have made a good faith effort herein to address all of the issues raised by the Examiner and place this application in form for allowance. if any additional issues need to be addressed prior to issuance of a notice of allowance, the Examiner is invited to call Applicants' attorney at the phone number below so that they can be worked out.

Respectfully submitted,
Frank P. Zemlan et al.

By _____
Steven J. Goldstein
Registration No. 28,079
Attorney for Applicants

FROST BROWN TODD LLC
2200 PNC Center
201 East Fifth Street
Cincinnati, Ohio 45202
(513) 651-6131

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Box Non-Fee Amendment, The Assistant Commissioner for Patents, Washington, D.C., 20231, this 12th day of March, 2002.

_____
Sarah Ohlweiler

CINlibrary/1157818.1

Appendix A
Marked Version Showing Changes Made

Claims 14, 17, 24 and 31 are amended as follows:

Claim 14 (four times amended), A method of determining axonal damage in the [central nervous system] head of a patient suspected of having a traumatic [central nervous system] head injury, said method comprising the steps:

(a) obtaining a sample of cerebrospinal fluid from said patient;

(b) treating said sample of cerebrospinal fluid with at least one monoclonal antibody, said at least one monoclonal antibody having been raised against an axonally-derived [protein in the form of an isoform of] tau protein of SEQ ID NO:1;

(c) detecting the presence of said axonally-derived tau protein bound to said at least one monoclonal antibody; and

(d) comparing the amount of said axonally-derived tau protein bound to said at least one monoclonal antibody in step (c) to control samples from the group representing a normal undamaged axon state and those representing an axonal damage state.

Claim 17 (four times amended). A method according to Claim 14 wherein said axonally-derived tau protein is a fragment of said tau protein of SEQ ID NO:1 demonstrating an apparent molecular weight in the range of [about] 30 kDa to [about] 50 kDa.

Claim 24 (four times amended). A method according to Claim 23 wherein said axonally-derived tau protein bound to said at least one monoclonal antibody is a fragment of tau protein SEQ ID NO:1 which is detected through gel electrophoresis and which gives rise to an electrophoresis gel demonstrating multiple protein [bonds] bands with apparent molecular weights from [about] 30 kDa to [about] 50 kDa.

Claim 31 (twice amended). A method of determining axonal damage in the [central nervous system] head of a patient suspected of having traumatic [central nervous system] head injury, said method comprising the steps of:

(e) obtaining a sample of cerebrospinal fluid from said patient;

(f) treating said sample of cerebrospinal fluid with at least one monoclonal antibody, said at least one monoclonal antibody having been raised against an axonally-derived [protein in the form of an isoforms of] tau protein of SEQ ID NO:1;

(g) detecting the presence of said axonally-derived tau protein bound to said at least one monoclonal antibody; and

(h) comparing the amount of said axonally-derived tau protein bound to said at least one monoclonal antibody in step (c) to control samples selected from the group representing a normal undamaged axon state and those representing an axonal damage state.

Missouri State Government Web

MISSOURI Head Injury Advisory Council

Home

What is Traumatic Head or Traumatic Brain Injury?

"Head injury" or "traumatic head injury" is defined as: "a sudden insult or damage to the brain or its coverings, not of a degenerative nature. Such insult or damage may produce an altered state of consciousness and may result in a decrease of one or more of the following: mental, cognitive, behavioral or physical functioning resulting in partial or total disability. Cerebral vascular accidents, aneurisms and congenital deficits are specifically excluded from this definition" (Section 192.735 RSMo).

Head injury or brain injury is a traumatic insult to the brain requiring extensive services over an extended period of time. Although the injury is not always visible, it may cause physical, emotional, intellectual, social and vocational changes. There are two types of head injury: closed head injury and open head injury. A "closed head injury" refers to damage that occurs within the skull after a blow to the head. Although the skull may stop on impact, the brain will often continue to whip back and forth against the skull from within causing damage. The second category of head injury referred to as "open head injury" is a visible assault and may be the result of a gun shot wound for example.

Back to "About Traumatic Brain Injury" Page

State of Missouri
Office of Administration
Division of General Services

Epidemiology of Traumatic Brain Injury in the United States

Of all types of injury, those to the brain are among the most likely to result in death or permanent disability. Estimates of traumatic brain injury (TBI) incidence, severity, and cost reflect the enormous losses to individuals, their families, and society from these injuries. These data demonstrate a critical need for more effective ways to prevent brain injuries and care for those who are injured.

Highlights

Incidence of traumatic brain injury (TBI). Using national data for 1995-1996, the CDC estimates that TBIs have this impact in the United States each year:

- 1 million people are treated and released from hospital emergency departments[1]
- 230,000 people are hospitalized and survive[2]
- 50,000 people die[3]

TBI incidence rate, risk factors, and causes. Using preliminary hospitalization and mortality data collected from 12 states (Alaska, Arizona, Sacramento County [California], Colorado, Louisiana, Maryland, Missouri, New York, Oklahoma, Rhode Island, South Carolina, and Utah) during 1995-1996, CDC finds the following:[4]

- The average TBI incidence rate (combined hospitalization and mortality rate) is 95 per 100,000 population. Twenty-two percent of people who have a TBI die from their injuries.
- The risk of having a TBI is especially high among adolescents, young adults, and people older than 75 years of age.
- For persons of all ages, the risk of TBI among males is twice the risk among females.
- The leading causes of TBI are motor vehicle crashes, violence, and falls. Nearly two-thirds of firearm-related TBIs are classified as suicidal in intent.
- The leading causes of TBI vary by age: falls are the leading cause of TBI among persons aged 65 years and older, whereas transportation leads among persons aged 5 to 64 years.
- The outcome of these injuries varies greatly depending on the cause: 91% of firearm-related TBIs resulted in death, but only 11% of fall-related TBIs are fatal.

Incidence and prevalence of TBI-related disability. Based on national TBI incidence data and preliminary data from the Colorado Traumatic Brain Injury Registry that describe TBI-related disability in 1996-1997, CDC estimates the following:[5]

- Each year more than 80,000 Americans survive a hospitalization for traumatic brain injury but are discharged with TBI-related disabilities.
- 5.3 million Americans are living today with a TBI-related disability.

Note: The preliminary estimates described above are derived from provisional data that are subject to change, pending receipt of additional data. Therefore, the information contained in this outline should not be published without approval from the Centers for Disease Control and Prevention.

Traumatic Brain Injury Incidence: Morbidity and Mortality

There are several published epidemiologic studies of TBI-related hospitalizations and deaths in the U.S. Kraus has reviewed some of these studies in detail.[6] Recent data suggest a decline in rates of hospitalization for less severe TBI, possibly due to changes in hospital admission criteria.[2] The lower TBI incidence rate seen today may be due in part to a real decline in brain injuries but also appear to be an artifact of counting methods which capture only hospitalized and fatal cases.

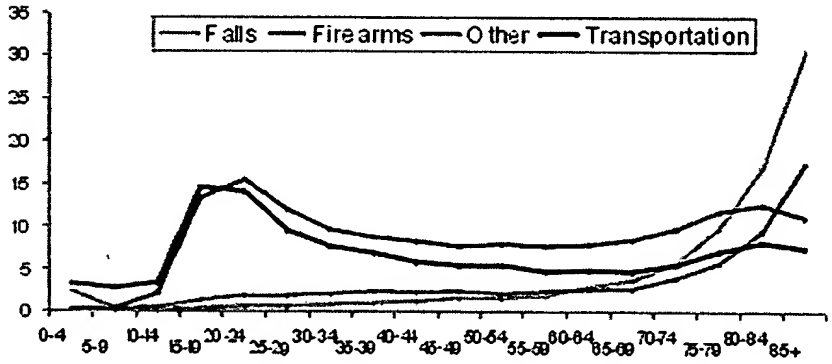
Location of Study	Year(s)	Annual Rate of TBI per 100,000 Population
Olmstead County, Minnesota[7]	1934-74	193
U.S.[8]	1974	200
San Diego, California[9]	1978	294
North Central Virginia[10]	1978	175
Rhode Island[11]	1979-80	249
Chicago, Illinois[12]	1980	367
Bronx, New York City, New York[13]	1980	249
San Diego County, California[14]	1981	180
Maryland[15]	1986	132
Utah[16]	1990-92	106
Colorado, Missouri, Oklahoma,	1990-93	103

Utah[17]		
Colorado[18]	1991-92	101
Seven states (AZ, CO, MN, MO, NY excluding NYC, OK, SC)[5,19]	1994	92

Traumatic Brain Injury Mortality: Causes and Trends

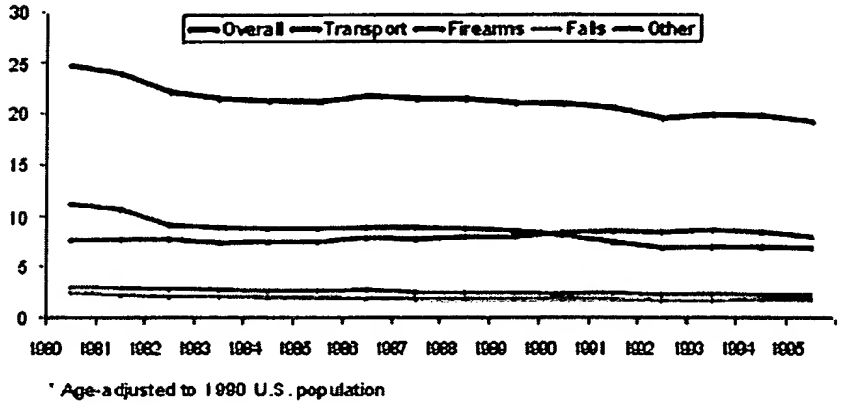
There was a 22% decline in the TBI-related death rate from 24.6/100,000 U.S. residents in 1979 to 19.3/100,000 in 1992.[20] Firearm-related rates increased 13% from 1984 through 1992, undermining a 25% decline in motor vehicle-related rates for the same period. Firearms surpassed motor vehicles as the largest single cause of death associated with traumatic brain injury in the United States in 1990. These data highlight the success of efforts to prevent traumatic brain injury due to motor vehicles and failure to prevent such injuries due to firearms. The increasing importance of penetrating injury has important implications for research, treatment, and prevention of traumatic brain injury in the United States.

Traumatic brain injury-related death rates by age and cause, U.S., 1995



* Age-adjusted to 1990 U.S. population

Traumatic Brain Injury-related death rates by cause, U.S., 1980-1995*



* Age-adjusted to 1990 U.S. population

Populations at Risk, Outcome and Cost

Populations at Risk

A number of studies have shown that males are about twice as likely to incur TBI as females. Most studies indicate that the highest rates of these injuries are found in persons 15-24 years of age. Persons under the age of 5 or over the age of 75 are also at high risk.

Outcome

Each year more than 50,000 Americans die following traumatic brain injuries.[3] Each year an estimated 80,000 Americans survive a hospitalization for traumatic brain injury but are discharged with TBI-related disabilities. An estimated 5.3 million Americans are living today with a TBI-related disability.[5]

There are many kinds of impairments that may occur as a result of TBI. These injuries may impair:

- cognition -- concentration, memory, judgment, and mood
- movement abilities -- strength, coordination, and balance
- sensation -- tactile sensation and special senses such as vision

TBI sometimes results in seizure disorders (epilepsy). About 1 percent of persons with severe TBI survive in a state of persisting unconsciousness.

Cost

There is no way to describe fully the human costs of traumatic brain

injury: the burdens borne by those who are injured and their families.

Only a few analyses of the monetary costs of these injuries are available, including the following estimate (lifetime cost of all brain injuries occurring in the United States in 1985):[21]

• Direct annual expenditures	$ 4.5 billion
• Indirect annual costs	$33.3 billion
• Total costs	$37.8 billion

Traumatic Brain Injury as a Public Health Problem

A large number of people experience traumatic brain injury each year, often with severe consequences. This is a public health problem that requires:

- **Ongoing surveillance to follow trends in the incidence, risk factors, causes, and outcomes of these injuries.** To promote TBI surveillance efforts, the National Center for Injury Prevention and Control (NCIPC):
  - developed ***Guidelines for the Surveillance of Central Nervous System Injury,*** a publication that sets forth standards and recommendations to improve coordination of central nervous system injury surveillance.[22] The surveillance standards provide case definitions for traumatic brain injury and spinal cord injury and a list of defined data elements to be collected for each case of injury.
  - provided funding to Alaska, Arkansas, Arizona, California, Colorado, Louisiana, Maryland, Minnesota, Missouri, Nebraska, New York, Oklahoma, Rhode Island, South Carolina, and Utah to enhance current traumatic brain injury surveillance by using the standards defined in the ***Guidelines for the Surveillance of Central Nervous System Injury.*** These states contribute data to a multi-state surveillance system maintained by the NCIPC.
- **The development of effective, science-based strategies to prevent the occurrence of these injuries.**[23] In collaboration with other federal and state agencies, the National Center for Injury Prevention and Control supports programs for the primary prevention of motor vehicle-related injuries, other unintentional injuries, and violence-related injuries.
- **The development of more effective strategies to improve the outcomes of these injuries and minimize disability among those injured.**[24] The National Center for Injury

Prevention and Control:

- provides funding to the Colorado Department of Public Health and the Environment (in collaboration with Craig Hospital) and the South Carolina Department of Health and Environmental Control (in collaboration with the University of South Carolina School of Medicine) to develop population-based follow-up registries of persons who have sustained traumatic brain injury. This project will determine the burden of disabilities, monitor trends in disabilities, identify subgroups of people with traumatic brain injury at highest risk of disability, and determine service utilization and barriers to service access.
- developed Facts about Concussion and Brain Injury to address the lack of information on the symptoms, sequelae and treatment of less severe TBI. This booklet explains what can happen after a concussion, how to get better, and where to go for more information and help when needed.
- funds cooperative agreements for Statewide Traumatic Brain Injury Surveillance Programs
- created the document, Traumatic Brain Injury in the United States: A Report to Congress, summarizing current knowledge about the incidence, causes, severity, associated disabilities, and prevalence of TBI.

References

1. Guerrero J, Thurman DJ, Sniezek JE. Emergency department visits association with traumatic brain injury: United States, 1995-1996. *Brain Injury*, 2000; 14(2):181-6.
2. Thurman DJ, Guerrero J. Trends in hospitalization associated with traumatic brain injury. *JAMA*, 1999; 282(10):954-7.
3. Unpublished data from Multiple Cause of Death Public Use Data from the National Center for Health Statistics, 1996. Methods are described in Sosin DM, Sniezek JE, Waxweiler RJ. Trends in death associated with traumatic brain injury, 1979-1992. *JAMA* 1995;273(22):1778-1780.
4. Analysis by the CDC National Center for Injury Prevention and Control, using data obtained from state health departments in Alaska, Arizona, California (reporting Sacramento County only), Colorado, Louisiana, Maryland, Missouri, New York, Oklahoma, Rhode Island, South Carolina, and Utah. Methods are described in:
    - Centers for Disease Control and Prevention. Traumatic Brain Injury -- Colorado, Missouri, Oklahoma, and Utah, 1990-1993. *MMWR* 1997;46(1):8-11.
    - Thurman DJ, Sniezek JE, Johnson D, Greenspan A, Smith SM. *Guidelines for Surveillance of Central*

Nervous System Injury. Atlanta: Centers for Disease Control and Prevention, 1995.

5. Thurman DJ, Alverson CA, Dunn KA, Guerrero J, Sniezek JE. Traumatic brain injury in the United States: a public health perspective. *J Head Trauma Rehab*, 1999; 14(6):602-15.
6. Kraus JF. Epidemiology of head injury. In: Cooper, PR, ed. *Head Injury,* Third Edition. Baltimore: Williams and Wilkins, 1993; 1-25.
7. Annegers JF, Grabow HD, Kurland LT, *et al.* The incidence, cause and secular trends in head injury in Olmstead County, Minnesota, 1935-1974. *Neurology* 1980;30:912-919.
8. Kalsbeek WD, McLaurin RL, Harris BS, Miller JD. The national head and spinal cord injury survey: Major findings. *Journal of Neurosurgery* 1980;53:S19-S24.
9. Klauber MR, Barrett-Connor E, Marshall LF, Bowers SA. The epidemiology of head injury: A prospective study of an entire community--San Diego County, California, 1978. *American Journal of Epidemiology* 1981;113:500-509.
10. Jagger J, Levine JI, Jane JA, Rimel RW. Epidemiologic features of head injury in a predominantly rural population. *Journal of Trauma* 1984;24:40-44.
11. Fife D, Faich G, Hollinshead W, Wentworth B. Incidence and outcome of hospital-treated head injury in Rhode Island. *American Journal of Public Health* 1986;76:773-778.
12. Whitman S, Coonley-Hoganson R, Desai BT. Comparative head trauma experience in two socioeconomically different Chicago-area commmunities: A population study. *American Journal of Epidemiology* 1984; 4:560-580.
13. Cooper KD, Tabaddor K, Hauser WA, *et al.* The epidemiology of head injury in the Bronx. *Neuroepidemiology* 1983;2:70-88.
14. Kraus JF, Black MA, Hessol N, *et al.* The incidence of acute brain injury and serious impairment in a defined population. *American Journal of Epidemiology* 1984;119:186-201.
15. MacKenzie EJ, Edelstein SL, Flynn JP. Hospitalized head-injured patients in Maryland: Incidence and severity of injuries. *Maryland Medical Journal* 1989:38:725-732.
16. Thurman DJ, Jeppson L, Burnett CL, *et al.* Surveillance of traumatic brain injuries in Utah. *West J Med* 1996;165:192-196.
17. Centers for Disease Control and Prevention. Traumatic brain injury -- Colorado, Missouri, Oklahoma, and Utah, 1990-1993. *MMWR* 1997;46(1):8-11.
18. Gabella B, Hoffman RE, Marine WW, Stallones L. Urban and rural traumatic brain injuries in Colorado. *AEP* 1997;7(3):207-212.
19. Thurman DJ, *et al.* Traumatic brain injury in the United States: A report to Congress. Atlanta, Centers for Disease Control and Prevention, 1999.
20. Sosin DM, Sniezek JE, Waxweiler RJ. Trends in death

associated with brain injury, 1979-1992. *JAMA* 1995;273:1778-80.

21. Max W, MacKenzie EJ, Rice DP. Head injuries: costs and consequences. *Journal of Head Trauma Rehabilitation* 1991;6 (2):76-91.
22. Thurman DJ, Sniezek JE, Johnson D, Greenspan A, Smith SM. *Guidelines for Surveillance of Central Nervous System Injury.* Atlanta: Centers for Disease Control and Prevention, 1995.
23. National Committee for Injury Prevention and Control. *Injury Prevention: Meeting the Challenge.* New York: Oxford University Press, 1989.
24. Pope AM, Tarlov AR, editors. *Disability in America: Toward a National Agenda for Prevention.* Washington, DC: National Academy Press, 1991.

Contact Information

National Center for Injury Prevention and Control
Mailstop F41
4770 Buford Highway NE
Atlanta, GA 30341-3724

Phone: 770.488.4031
Fax: 770.488.4338
Email: DARDINFO@cdc.gov